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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,836	02/16/2006	Masaya Imoto	37404-78030	8924

23643 7590 06/29/2007

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,836	IMOTO ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *1-3,7-11 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/13/05,08/31/06,02/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 5-6 and 12, in the reply filed on 05/07/2007 is acknowledged. The traversal is on the ground(s) that the restriction of RNAi as a separate invention is improper and should be combined with the inventions comprising an antisense, a ribozyme and a maxizyme because the compounds are all equivalent to one of skill in the art as substances that suppress gene expression. Applicant's arguments are found persuasive and RNAi will be included with the group comprising antisense, ribozymes and maxizymes.

Status of the Application

Claims 1-13 are pending. Claims 4-6 and 12 are currently under examination. Claims 1-3, 6-11 and 13 are withdrawn as being drawn to a non-elected invention.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures: Figure 2 and 3 of the drawings recite a

sequence that does not have the required sequence identifier in either the drawing or the brief description of the drawing on page 5 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5 and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a substance for inhibiting expression of a PDGF receptor alpha gene wherein the substance is "an RNAi". RNAi is described in the specification as "a technique using double-stranded RNA (dsRNA) that induces a phenomenon called RNA interference". Therefore, it is unclear how a substance can be a process or technique. For purposes of prior art, a substance comprising "RNAi" is interpreted to mean a substance comprising a dsRNA.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing expression of the

PDGF receptor alpha gene using an antisense compound *in vitro*, does not reasonably provide enablement for a method of suppressing expression of a PDGF receptor alpha gene *in vivo* using antisense or RNAi. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to a method of suppressing PDGF receptor alpha gene expression using a substance that targets the mRNA of said gene. Further, the instant claims recite a therapeutic method for treating cancer comprising suppressing a PDGF receptor alpha gene expression using a substance that targets the mRNA of said gene.

The specification as filed discloses a method of inhibition of expression from a PDGF receptor alpha gene using an antisense compound targeted to said gene (see page 15). The specification further discloses a prophetic method of decreasing expression of PDGF receptor alpha gene in cancer cells of a mouse (see page 15). The specification does not teach a method of inhibition of expression from a PDGF receptor alpha gene using any substance, namely an antisense compound or RNAi wherein suppression of said gene is inhibited or treatment of cancer occurs *in vivo*.

There is no guidance in the specification as filed that teaches how to target the claimed antisense or RNAi agents to mammalian cells or tissues *in vivo* or inhibit the expression of PGDF receptor alpha gene in mammalian cells or tissues *in vivo*. Although the specification discloses inhibition of PDGF receptor alpha gene expression in cells using an antisense compound, such a disclosure would not be considered

enabling for *in vivo* delivery and treatment since the state of antisense and RNAi-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 4-6 and 12 encompass a method for delivering a broad range of inhibitor agents to any mammal, *in vivo*, to inhibit a broad range of PGDF receptor alpha genes in mammalian cells. Although the specification discloses inhibition of PDGF receptor alpha gene expression in cells using an antisense compound, this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense and RNAi. Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents.

Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2). The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).

The state of the art for therapeutic *in vivo* applications for RNAi face similar hurdles as antisense as observed by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph). Novina et al. (Nature 2004, Vol.430:161-164) agrees that the "major obstacle to therapeutic gene silencing is the 'delivery problem'- the necessity of introducing short dsRNAs into specific organs" (see page 164, third paragraph).

Paroo et al. (Trends in Biotechnology 2004, Vol.22(8):390-394) summarizes by stating "[d]eveloping siRNA for efficient gene silencing in vivo is likely to be more challenging and many issues must be addressed before use in animals can become routine. As with any compound, issues of adsorption, distribution, metabolism and excretion are significant obstacles. However, the duplex nature of siRNA introduced an additional layer of complexity. Even with the great progress that has been made, it is not clear whether or not siRNA possesses any advantages relative to traditional antisense oligonucleotides for in vivo experiments or therapeutic development. Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Although RNAi has been seen as the new magic bullet to silence genes, "...magic bullets need magic guns" (stated by William Pardridge as quoted by Adams in The Scientist (2005) Vol.19:Issue1). Adams notes that researchers have struggled to get their therapies to particular targets and as stated by McCaffrey "[t]heir approach involves injecting large amounts of virus [vectors expressing shRNA] into the tail vein of mice, or into an artery leading to the liver. Its efficient but probably isn't going to work for humans" (see page 2 The Scientist (2005) Vol.19:Issue1). Even some of the applicants of the instant application have noted the unpredictability of using siRNA injected into the vein and observes that "[i]n some cells, inhibition seemed nearly complete, whereas in others, low or moderate levels of EGFP were observed....These results may be due to incomplete inhibition in cells that take up lesser amounts of siRNA. High pressure delivery of fluorescently labeled siRNA reveals that in vivo

uptake is not equal in all hepatocytes when this method is used' (Lewis et al. Nature Genetics 2002 Vol.32;107-108).

As outlined above, it is well known that there is a high level of unpredictability in the antisense and RNAi art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely inhibiting expression of a target endogenous gene *in vivo* by delivering polynucleotides to cells via injection into vessels. Delivery and inhibition of a luciferase marker gene in pig cells, as shown in the specification (Examples 1, 4 and 5) does not correlate with the ability to inhibit any endogenous gene expressed in mammalian heart cells

While one skilled in the art may be able to produce a antisense compound or RNAi agent targeted to a PDGF receptor alpha gene in mammalian cells and inhibit gene expression in said cells, the specification as filed does not teach a method for delivering any inhibitory agent, specifically antisense or a RNAi agent, to inhibit expression of any PDGF receptor alpha gene from cell.

In view of the unpredictability in the art of antisense and RNAi-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of any inhibitor agene or specifically antisense or RNAi, *in vivo* by the broadly disclosed methodologies of the instantly

claimed invention, would result in successful inhibition of expression of an endogenous gene in mammalian cells. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the nucleic acid inhibitory agent *in vivo*, delivery of the nucleic acid, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Souza et al. (Development 1995, Vol. 121: 2559-2567).

The instant claims are drawn to a method of suppressing expression of the PDGF receptor alpha gene comprising targeting mRNA including exon 1 beta using a substance that targets the mRNA.

Souza et al. teach a method of inhibiting the expression of a PDGF receptor alpha gene using an antisense compound targeted to the mRNA of said gene (see page 2560), wherein said mRNA includes the exon 1 Beta region.

Thus, Souza et al. anticipates claims 4-6.

Claims 4-6 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by Heinrich et al. (US 2006/0084142).

The instant claims are drawn to a method of suppressing expression of the PDGF receptor alpha gene comprising targeting mRNA including exon 1 beta using a substance that targets the mRNA and drawn to a therapeutic method for treating cancer using an agent for suppressing expression of PDGF receptor gene.

Heinrich et al. teach a method of inhibiting the expression of a PDGF receptor alpha gene using an antisense compound targeted to the mRNA of said gene. Heinrich et al. teach the antisense compound can be also targeted to the encoding regions of the mRNA or the flanking regions (which includes the exons outside of the coding region (i.e. exon 1) (see paragraph 0247 and 0023). Heinrich et al. teach PDGF receptor alpha is involved in cancer, specifically glioma, and teach methods of treating cancer

comprising inhibiting suppression of expression from a PDGF receptor alpha gene (see paragraphs 0004-0008).

Thus, Heinrich et al. anticipates claims 4-6 and 12 of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-6 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinrich et al. (2006/0084142) as applied to claims 4 and 12 above, and further in view of Hammond et al. (Nature Reviews Genetics February 2001) and Tuschl et al. (WO 02/44321).

The instant claims are drawn to a method of suppressing expression of the PDGF receptor alpha gene comprising targeting mRNA including exon 1 beta using a substance that targets the mRNA, wherein the substance is a dsRNA or a DNA that encodes a dsRNA and drawn to a therapeutic method for treating cancer using an agent for suppressing expression of PDGF receptor gene.

Heinrich et al. is relied upon as above. Heinrich et al. do not teach inhibiting the expression the PDGF receptor alpha gene using a dsRNA.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. teach dsRNA molecules and teach compositions comprising siRNA and an acceptable carrier that are capable of silencing gene expression (see page 9, lines 17-25). Tuschl et al. teach that dsRNAs represent a new alternative to antisense or ribozyme therapeutics.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a dsRNA molecule, as taught by Hammond et al. and Tuschl et al. to target a gene encoding PDGF receptor alpha, as taught by Heinrich et al.

One would have been motivated to use a siRNA targeted to a PDGF receptor alpha gene and inhibit gene expression because Heinrich et al. teach PDGF receptor alpha expression is involved in cancer. One would have been motivated to use a siRNA targeted to a PDGF receptor alpha gene instead of an antisense because it was well known at the time the invention was made that siRNA molecules are efficient molecules to target and decrease expression of a target gene and because Hammond et al. teach using siRNA to inhibit gene expression is more sequence specific than using antisense

methodologies and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell. One would have been motivated to create such compounds with increased stability and functionality, and since dsRNAs are taught by Tuschl et al. as being useful in silencing gene expression.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any dsRNA to any gene provided the target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

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